

VU Research Portal

Association of polygenic score for major depression with response to lithium in patients with bipolar disorder

Amare, Azmeraw T; Baune, Bernhard T; Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium; Abdellaoui, A.; Dolan, C.V.; Hottenga, Jouke Jan ; Mbarek, Hamdi; Middeldorp, C.M.; Nivard, Michel G.; Willemsen, Gonneke; Boomsma, D.I.; de Geus, Eco J.C.; Beekman, Aartjan F T; Jansen, Rick; Milaneschi, Yuri; Peyrot, Wouter J; Smit, Johannes H.; W J H Penninx, Brenda; Posthuma, Danielle

published in

Molecular Psychiatry

2021

DOI (link to publisher)

[10.1038/s41380-020-0689-5](https://doi.org/10.1038/s41380-020-0689-5)

document version

Publisher's PDF, also known as Version of record

document license

Article 25fa Dutch Copyright Act

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Amare, A. T., Baune, B. T., Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Abdellaoui, A., Dolan, C. V., Hottenga, J. J., Mbarek, H., Middeldorp, C. M., Nivard, M. G., Willemsen, G., Boomsma, D. I., de Geus, E. J. C., Beekman, A. F. T., Jansen, R., Milaneschi, Y., Peyrot, W. J., Smit, J. H., W J H Penninx, B., & Posthuma, D. (2021). Association of polygenic score for major depression with response to lithium in patients with bipolar disorder. *Molecular Psychiatry*, 26(6), 2457-2470. <https://doi.org/10.1038/s41380-020-0689-5>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:

vuresearchportal.ub@vu.nl



Association of polygenic score for major depression with response to lithium in patients with bipolar disorder

Azmeraw T. Amare ^{1,2} et al.

Received: 22 November 2018 / Revised: 28 January 2020 / Accepted: 13 February 2020
© The Author(s), under exclusive licence to Springer Nature Limited 2020

Abstract

Lithium is a first-line medication for bipolar disorder (BD), but only one in three patients respond optimally to the drug. Since evidence shows a strong clinical and genetic overlap between depression and bipolar disorder, we investigated whether a polygenic susceptibility to major depression is associated with response to lithium treatment in patients with BD. Weighted polygenic scores (PGSs) were computed for major depression (MD) at different GWAS *p* value thresholds using genetic data obtained from 2586 bipolar patients who received lithium treatment and took part in the Consortium on Lithium Genetics (ConLi⁺Gen) study. Summary statistics from genome-wide association studies in MD (135,458 cases and 344,901 controls) from the Psychiatric Genomics Consortium (PGC) were used for PGS weighting. Response to lithium treatment was defined by continuous scores and categorical outcome (responders versus non-responders) using measurements on the *Alda* scale. Associations between PGSs of MD and lithium treatment response were assessed using a linear and binary logistic regression modeling for the continuous and categorical outcomes, respectively. The analysis was performed for the entire cohort, and for European and Asian sub-samples. The PGSs for MD were significantly associated with lithium treatment response in multi-ethnic, European or Asian populations, at various *p* value thresholds. Bipolar patients with a low polygenic load for MD were more likely to respond well to lithium, compared to those patients with high polygenic load [lowest vs highest PGS quartiles, multi-ethnic sample: OR = 1.54 (95% CI: 1.18–2.01) and European sample: OR = 1.75 (95% CI: 1.30–2.36)]. While our analysis in the Asian sample found equivalent effect size in the same direction: OR = 1.71 (95% CI: 0.61–4.90), this was not statistically significant. Using PGS decile comparison, we found a similar trend of association between a high genetic loading for MD and lower response to lithium. Our findings underscore the genetic contribution to lithium response in BD and support the emerging concept of a lithium-responsive biotype in BD.

Introduction

Bipolar disorder (BD) is a chronic and severe psychiatric illness characterized by episodic, abnormal manic and depressive mood states. An estimated 48.8 million people are affected by

BD globally [1]. The disorder accounts for 9.9 million years of life lived with disability worldwide, and substantially increases all-cause mortality and risk of suicide [1, 2].

Amongst available treatment options, lithium is regarded as a gold standard by several clinical guidelines [3, 4]. Lithium uniquely protects against both manic and depressive illness phases, has demonstrated protective effects against suicide [5–7], and is particularly effective in preventing rehospitalization [8]. However, not all patients with BD fully benefit from lithium and only about 30% show full response to the drug [5–7]. In current psychiatric practice, no biological or clinical markers exist that could reliably predict responsiveness to lithium [9], and prescribing cannot be targeted to patients who benefit most while avoiding side effects and sub-optimal treatment for poor responders [10–13].

In order to develop objective response markers and to move forward towards personalized prescribing of lithium

These authors contributed equally: Azmeraw T. Amare, Klaus Oliver Schubert

Members of the Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium are listed below acknowledgments.

Supplementary information The online version of this article (<https://doi.org/10.1038/s41380-020-0689-5>) contains supplementary material, which is available to authorized users.

✉ Bernhard T. Baune
bernhard.baune@ukmuenster.de

Extended author information available on the last page of the article

for BD patients, a better understanding of the biological mechanisms underlying lithium response is urgently required. Recent genome-wide association studies (GWAS) carried out by our International Consortium on Lithium Genetics (ConLi⁺Gen) [5] and others [14, 15] have indicated that genetic variation could be an important mediator of response to long-term lithium treatment response in BD patients. In addition, we have recently demonstrated that high genetic loading for schizophrenia (SCZ) risk variants in people with BD decreases the likelihood of favorable response to lithium [16], suggesting that polygenic score (PGS) analysis of mental and physical traits could yield important information on the genetic architecture of BD phenotypes [17–19].

BD and MD show 47% genetic overlap [20–22], and shared risk genes and biological pathways have been described [21, 23, 24]. Lithium can be effective as an augmentation strategy in MD patients who have experienced an insufficient response to first-line antidepressants [25, 26] and is protective against further MD episodes after symptom remission has been achieved [27]. Moreover, a large observational study based on the Finnish registry showed that lithium is the most effective agent preventing rehospitalization in MD [27].

On the other hand, in BD, lithium is more effective in preventing manic than depressive episodes [28, 29], leading to the notion that better lithium responders might be more likely to experience manic predominant polarity, as opposed to depressive predominant polarity [30]. In support of this view, one study found that excellent lithium responders were characterized by a manic but not depressive polarity of the index episode [31]. Another study described an episodic illness pattern of ‘mania-depression-interval’ as a predictor for a good response, whereas a ‘depression-mania-interval’ predicted poorer outcomes [32]. Inter-episode residual mood symptoms, as opposed to full remission [6, 7, 33], a rapid cycling pattern [32, 33], and a history of mixed episodes [34, 35] have also been described as predictors of poor response.

On the background of these complex interactions between BD, MD, and lithium treatment, we asked whether BD patients with a high genetic susceptibility for major depression, expressed by their PGS, would respond better or worse to lithium than BD patients with a low genetic loading [36].

Methods and materials

Discovery GWAS summary dataset

The polygenic score for this study was computed using individual genetic data from the International Consortium on Lithium Genetics (ConLi⁺Gen) [5], and GWAS

summary statistics for MD from the Psychiatric Genomics Consortium (PGC) [36].

The summary GWAS for MD was produced from a meta-analysis of 9.6 million SNPs (PGC; <http://www.med.unc.edu/pgc/>), obtained from 7 cohorts (deCODE, Generation Scotland, GERA, iPSYCH, UK Biobank, PGC29 and 23andMe) containing 135,458 MD cases and 344,901 healthy controls [36].

Target study sample

For the PGS analysis, clinical data on lithium treatment response and genetic information were obtained from the International Consortium on Lithium Genetics (ConLi⁺Gen; www.ConLiGen.org) for $n = 2586$ patients, including 23 patients in the replication sample [3, 5, 16]. A series of quality control procedures were implemented on the genotype data before and after imputation as described below.

Target outcome

Lithium treatment response was assessed using the validated “Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder” scale, also known as the *Alda* scale [7, 37, 38]. This scale quantifies symptom improvement over the course of treatment (A score, range 0–10), which is then weighted against five criteria (B score) that assess the quality of evidence for the response score [5], to arrive at a total *Alda* score. For dichotomized assessment of treatment response, patients with a total score of 7 or higher were categorized as “good responders”, and the remainder were categorized as poor responders [5, 38]. For continuous assessment of treatment response, *Alda* A scores were used [39]. In addition to the *Alda* scale scores, information on covariates such as age and gender was collected, as described in detail elsewhere [5].

Genotyping and quality control

The genome-wide genotypes, as well as clinical and demographic data, were collected by 22 participating sites. Quality control (QC) procedures were implemented on the genotype data using PLINK, version 1.09 prior to imputation [40]. Samples with low genotype rates (<95%), sex inconsistencies (based on X-chromosome heterozygosity), and one of a pair of genetically related individuals were excluded. SNPs were excluded based on the following criteria: a poor genotyping rate (<95%), strand ambiguity (A/T and C/G SNPs), a low minor allele frequency (MAF < 1%), or those deviated from genotype frequency expectations under the Hardy–Weinberg Equilibrium ($p < 10^{-6}$).

Imputation

The genotype data passing QC were imputed on the Michigan server [41] (<https://imputationserver.sph.umich.edu>) separately for each genotype platform using reference data from the 1000 Genomes Project Phase 3 (Version 5). The European reference panel was used for all the samples except for those from Japan and Taiwan, for which an East Asian reference population data was used. After excluding low-frequency SNPs ($MAF < 10\%$); low-quality variants (imputation $INFO < 0.9$); and indels, the imputed dosages were converted to best-guess genotypes. The subsequent polygenic analyses were performed using these best-guess genotypes.

Statistical analyses

Polygenic score (PGS) association analysis

PGSs were calculated using the approach previously described by the International Schizophrenia Consortium [42]. Prior to the PGS computation, independent SNPs were identified through a clumping procedure. Quality-controlled SNPs were clumped for linkage disequilibrium based on GWAS association p value informed clumping at $r^2 = 0.1$ within a 250-kilobase window to create an SNP-set in linkage equilibrium using PLINK software, version 1.09 run on Linux (`plink --clump-p1 1 --clump-p2 1 --clump-r2 0.1 --clump-kb 250`). PGSs of MD were calculated for each patient in the ConLi⁺Gen sample at ten p value thresholds ($< 1 \times 10^{-4}$, $< 1 \times 10^{-3}$, < 0.01 , < 0.05 , < 0.1 , < 0.2 , < 0.3 , < 0.4 , < 0.5 , < 1). For a patient, a PGS was calculated at each p value threshold (P_T) as the sum of allelic counts (from 0 to 2) for the reference alleles across independent SNPs on a genome-wide scale weighted by their effect sizes estimated as beta or log10 (odds ratio), obtained from previously published GWASs of MD [36].

Once the PGSs were constructed, a binary logistic regression model was applied for the binary outcome (lithium response versus non-response) and a linear regression modeling was implemented for the continuous outcome (*Alda* score on subscale A) to evaluate the association of the PGSs for MD with lithium treatment response at each P_T . Using the PGS at the most optimal thresholds, we divided the study samples into quartiles and deciles, ranging from the lowest polygenic load (1st quartile or 1st decile) to the highest polygenic load (4th quartile or 10th decile). Then, we compared BP patients in the lower polygenic load quartiles (1st–3rd quartiles or 1st–9th deciles) with patients in the highest polygenic load quartile (4th quartile or 10th decile), to quantify the effect of MD polygenic load on lithium treatment response. The

analysis was performed for the European sample ($N = 2366$), Asian sample ($N = 220$) and all the sample combined ($N = 2586$). Associations were considered significant at $p < 0.05$ after adjusting for covariates.

The PGS association analyses were adjusted for the covariates age, gender, genotyping platform, a polygenic score for schizophrenia [16], a polygenic score for bipolar disorder [43], and seven principal components (PCs) in the combined sample or five PCs in the European sample or four PCs in the Asian sample. The PCs were computed using a `--pca` command in PLINK and then the top PCs with an eigenvalue of > 2.0 were extracted and used as covariates to correct for population stratification. The analyses were performed using R for Statistical Computing and PLINK, version 1.09 for Linux [40]. Prediction accuracy, the percentage of variance in lithium response accounted for by the PGS at each P_T , was estimated as the variance explained by the full model including each PGS and covariates minus the variance explained by the model including only covariates.

Sensitivity analysis

To evaluate the robustness of our findings, we ran sensitivity analyses using GWAS summary data from bone traits [lumbar spine bone mineral density, femoral neck mineral density and forearm bone mineral density] [44] that have previously shown nonsignificant genetic correlations with psychiatric disorders [45]. Once we compute polygenic scores for lumbar spine bone mineral density, femoral neck mineral density and forearm bone mineral density, we evaluated its association with lithium treatment response, both continuous and categorical outcomes, in the combined sample ($N = 2586$). Each analysis was adjusted for covariates age, gender, genotyping platform, polygenic score for schizophrenia [16], polygenic score for bipolar disorder [43] and seven PCs.

Results

Sample characteristics and lithium treatment response rate

After QC, 2586 patients (3193 before QC) remained for analysis. While $n = 2366$ were of European ancestry, the remaining ($n = 220$) were of Asian ancestry. In all, 704 patients (27.2%) responded optimally to lithium treatment (total *Alda* score ≥ 7). Detailed sample and demographics details have been described previously [16]. Analysis of the correlation between the PGSs for MD and the self-reported number of depressive episodes available for a

subset of the ConLi⁺Gen sample ($N = 1140$) showed a statistically significant positive correlation, with estimates ranging from 0.08 to 0.12, suggesting that the PGS for MD may be an approximation to a more severe depressive phenotype in BD (Supplementary Fig. 1).

The polygenic score for MD is inversely associated with lithium treatment response in BD

Statistically significant associations were found at various p value thresholds between the PGSs for MD and lithium treatment response. In the combined multi-ethnic sample, the strongest association were found at $P_T < 5 \times 10^{-2}$; $p < 0.001$, $R^2 = 0.8\%$ with the continuous outcome (*Alda* A score) and $p < 0.001$, $R^2 = 0.7\%$ with the categorical outcome (total *Alda* score ≥ 7) (Fig. 1a).

In European ancestry patients, the PGS at most of the tested p value thresholds showed significant associations of MD PGS with lithium response across continuous and dichotomized outcomes. Strongest associations were found at $P_T < 5 \times 10^{-2}$; $p < 0.001$, $R^2 = 0.7\%$ with the continuous outcome and $p < 0.001$, $R^2 = 0.9\%$ with the categorical outcome (Fig. 1b). However, in the Asian subsample, the association of the PGS for MD and lithium treatment response was less robust and marginal associations were found only with the continuous outcome at $P_T < 1 \times 10^{-2}$ ($p = 0.034$, $R^2 = 0.85\%$) and $P_T < 5 \times 10^{-2}$ ($p = 0.042$, $R^2 = 0.75\%$) (Fig. 1c). Using PRSice2 software, we found consistent results of association between the PGSs for MD and lithium treatment response [46] (Supplementary Fig. 2A–C). After adjusting for multiple testing using the Bonferroni method [47], associations remained statistically significant in the multi-ethnic and European sample, but not in the Asian sample (Supplementary Table 1). Beta coefficients for all associations were negative, indicating that high genetic loadings for MD are associated with poorer response to lithium in BD.

To further evaluate the impact of MD PGS on lithium treatment response, we divided the study population into quartiles and deciles based on their polygenic loading for MD. As shown in Fig. 2 and Table 1, BD patients who carry a lower polygenic load (1st quartile or 1st decile) for MD have higher odds of favorable lithium treatment response, compared to patients carrying a high polygenic load (4th quartile or 10th decile). In the combined sample, the odds ratio (OR) of favorable response for patients in the 1st quartile compared with those in the 4th quartile was 1.54 (95% CI: 1.18–2.01) and the OR of patients in 1st decile compared to the 10th decile was 1.49 (95% CI: 0.97–2.31). Stratified analysis by ethnicity found a stronger association in the European sample than the Asian sample (Table 1, Fig. 2 & Supplementary Fig. 3).

Sensitivity analysis

To ensure the robustness of our findings, we performed a sensitivity analysis and found no significant association between the polygenic scores for lumbar spine bone mineral density, femoral neck mineral density or forearm bone mineral density and lithium treatment response in bipolar patients, $p > 0.05$ for all polygenic score association tests at different p value thresholds (Supplementary Fig. 4A–C).

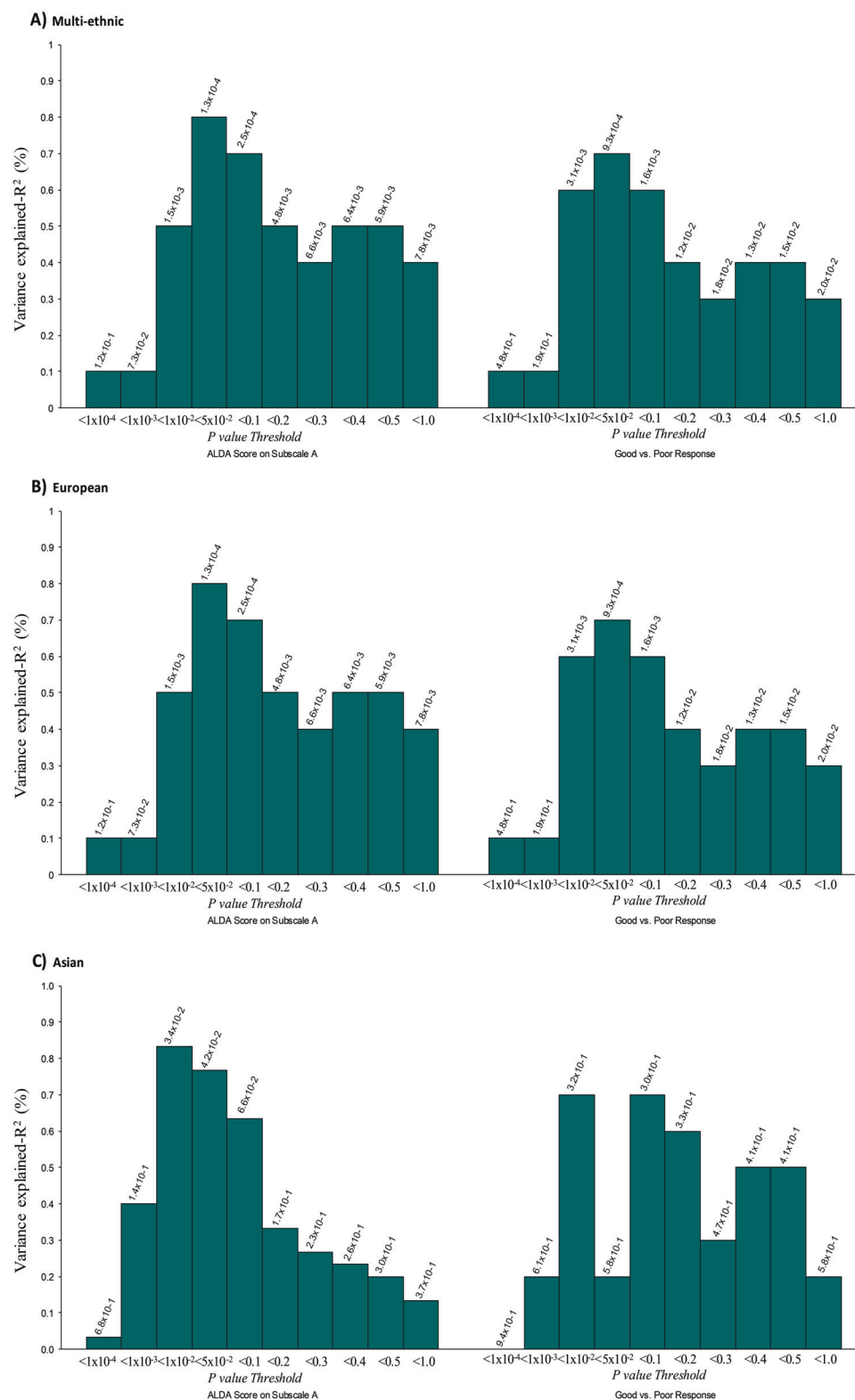
Discussion

Our study represents the first direct molecular evidence of an association between a genetic predisposition for major depression and poorer response to lithium treatment in patients with BD. Using PGS analyses of genetic variants related to MD, we found that BD patients with *low* genetic loading for these variants were about 1.5 times *more* likely to have favorable long-term outcomes following lithium treatment compared to BD patients with high MD genetic loading. Higher MD PGSs were associated with a higher number of reported life-time depressive episodes. Analyses following stratification of our sample into European and Asian ancestries indicated that these associations were particularly robust in the European subsample. Adjustment for the potential effects of psychiatric traits that show genetic overlap with MD (SCZ, BD), and sensitivity analyses with medical traits that are unrelated to psychiatric disorders [44] underscored the overall robustness of our findings.

Our findings could form part of a genetic explanation for the previously described clinical observations in relation to mania, depression and lithium response in BD [6, 7, 28–35] and supports the notion that better lithium responsiveness could be associated with a ‘core’ bipolar phenotype in the *Kraepelinian* form of manic depression [35, 48], characterized by a predominant mania-depression-interval (MDI) sequence pattern [49, 50]. The fact that such a phenotype is complex and difficult to clinically identify is exemplified by the lack of meta-analytic evidence for a more straightforward association between lithium response and mania over depression dominance in BD [50]. Similarly, previous family studies found no association between a family psychiatric history of MD and poorer lithium response in BD [51].

Together with the previously reported inverse association of lithium response and schizophrenia PGS [16], in the same cohort, our finding suggests that the presence of psychiatric co-morbid genetic traits in BD diminishes the likelihood of optimal treatment response to lithium. Given the substantial overlap between schizophrenia- and MD risk alleles [43], the possibility that these effects are driven by similar molecular mechanisms warrants further clarification in future studies.

Fig. 1 The association of PGS for major depression (MD) and lithium treatment response at different GWAS p value thresholds. The y-axis refers to the percentage of variance in treatment response to lithium accounted for by the PGSs for MD at particular p value thresholds. On the x-axis, are the GWAS p value thresholds used to select single-nucleotide polymorphisms for the PGSs. On the top of each bar are the p values for the association between the PGSs for MD and lithium treatment response. Beta coefficients (not shown) were negative for all associations, indicating an inverse effect of MD PGS on lithium response.



In addition to its effects in BD, lithium's effectiveness as an adjunct antidepressant treatment for people with treatment-resistant MD is well established [52–58], and lithium is a first-line treatment for BD type 2 that shows a substantial genetic

overlap with MD [59]. Therefore, our finding raises the intriguing possibility that lithium possesses specific antidepressant mechanisms of action that are different from the mechanisms conferring long-term treatment response in BD.

Fig. 2 Odds ratios (ORs) for favorable treatment response to lithium in patients with BD. ORs are derived by comparing BD patients with the low major depression (MD) polygenic load deciles (1st–9th) with patients with the highest MD polygenic load (10th decile), estimated at the most significant p value thresholds ($n = 2586$).

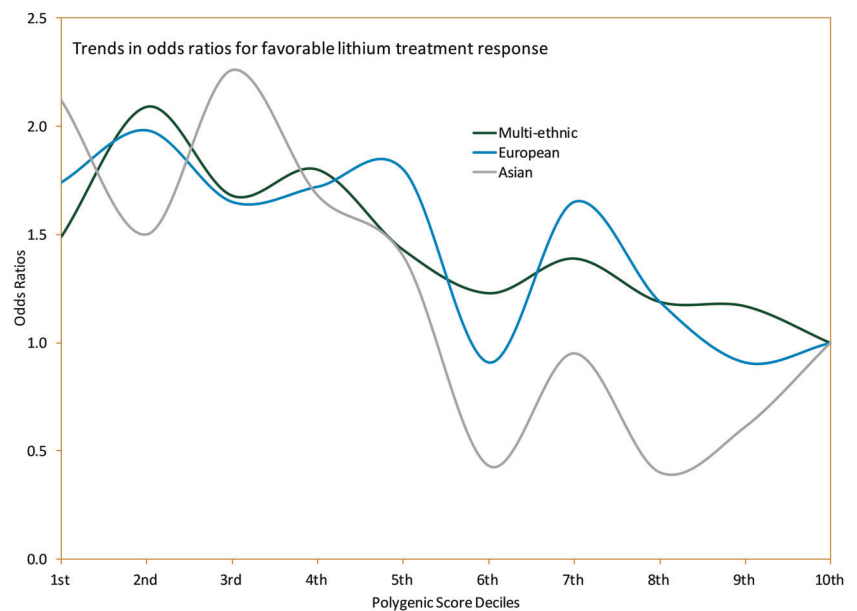


Table 1 Odds ratios of favorable lithium treatment response in patients with BD—comparing the response status of patients in the low polygenic score (PGS) quartile or decile for MD with patients with the highest polygenic load (4th quartile or 10th decile).

Categories	Multi-ethnic ($N = 2586$)		European ($N = 2366$)		Asian ($N = 220$)	
	Unadjusted OR (95% CI)	^a Adjusted OR (95% CI)	Unadjusted OR (95% CI)	^a Adjusted OR (95% CI)	Unadjusted OR (95% CI)	^a Adjusted OR (95% CI)
Quartile						
1st: lowest score	1.50(1.17–1.92)	1.54(1.18–2.01)	1.86(1.41–2.47)	1.75(1.30–2.36)	1.43(0.55–3.79)	1.71(0.61–4.90)
2nd	1.45(1.13–1.86)	1.46(1.12–1.90)	1.81(1.37–2.40)	1.77(1.31–2.38)	1.54(0.60–4.04)	1.74(0.64–4.85)
3rd	1.16(0.90–1.49)	1.12(0.85–1.47)	1.25(0.94–1.66)	1.21(0.89–1.64)	0.63(0.21–1.81)	0.55(0.17–1.66)
4th: highest score	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Decile						
1st: lowest score	1.50(1.00–2.27)	1.49(0.97–2.31)	1.92(1.23–2.99)	1.74(1.08–2.81)	1.77(0.40–8.52)	2.12(0.41–12.13)
2nd	2.06(1.39–3.09)	2.09(1.38–3.20)	2.10(1.35–3.28)	1.98(1.24–3.18)	1.25(0.27–6.08)	1.50(0.28–8.61)
3rd	1.76(1.18–2.64)	1.68(1.10–2.59)	1.90(1.22–2.96)	1.65(1.03–2.66)	1.62(0.37–7.73)	2.26(0.46–12.55)
4th	1.84(1.23–2.75)	1.80(1.18–2.77)	1.77(1.14–2.77)	1.72(1.08–2.78)	1.25(0.27–6.08)	1.68(0.33–9.44)
5th	1.49(1.00–2.25)	1.43(0.93–2.20)	1.92(1.23–2.99)	1.80(1.13–2.90)	1.25(0.27–6.08)	1.40(0.28–7.49)
6th	1.38(0.92–2.10)	1.23(0.80–1.92)	1.00(0.63–1.59)	0.91(0.56–1.50)	0.41(0.05–2.43)	0.43(0.05–2.87)
7th	1.39(0.92–2.10)	1.39(0.90–2.15)	1.65(1.06–2.58)	1.65(1.03–2.66)	0.93(0.18–4.68)	0.95(0.17–5.46)
8th	1.30(0.86–1.97)	1.19(0.77–1.85)	1.36(0.87–2.14)	1.19(0.74–1.94)	0.41(0.05–2.43)	0.40(0.04–2.74)
9th	1.25(0.82–1.90)	1.17(0.75–1.81)	0.92(0.57–1.47)	0.91(0.56–1.50)	1.25(0.27–6.08)	0.61(0.12–3.34)
10th: highest score	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)

The references (4th quartile and 10th decile) are the PGSs categories with the highest polygenic load for MD at the most significant threshold.

^aAdjusted for the covariates age, gender, genotyping platform, PGS for schizophrenia [16], PGS for bipolar disorder [43], and seven principal components (PCs) in the combined sample or five PCs in the European sample or four PCs in the Asian sample. OR odds ratio.

Our finding of a more robust effect of the MD PGS association with lithium response in European compared to Asian patients is interesting but needs to be interpreted with caution. First, our Asian subsample was small ($n = 220$) and may not have been powered sufficiently to detect more consistent effects. Second, the polygenic basis of

MD in East Asian and European populations is only partially shared with reported trans-ancestry genetic correlation of 0.33–0.41 [60]. The projection of MD risk alleles obtained from the global PGC study onto the Asian ConLi⁺Gen cohort for PGS analysis may, therefore, be less precise and underestimate the true MD PGS effect. It

is notable that ethnic differences with regards to lithium response have not been studied extensively and are not supported by a smaller previous study [61].

The main limitation of our study is that PGSs for MD explain only a small proportion of the variance in lithium treatment response (<1%), and on their own have no utility as clinical tests. However, since we detected significant effects in our relatively small sample, it is likely that in the future increased sample sizes will further improve the predictive power of PGSs [62]. Further, the current version of the *Alda* scale assesses only overall lithium efficacy but not effects specific to predominant illness polarity or episode sequence pattern. Availability and incorporation of such information would have refined our results. While our findings, in isolation, are not yet ripe for clinical applications, they could serve as a component of multimodal prediction models incorporating clinical and other biological data. The development of such models and the demonstration of their potential clinical utility in prospective study designs are beyond the scope of the current investigation but need to be attempted to translate our research findings into actionable clinical applications.

In conclusion, we demonstrated that high genetic loadings for MD are predictive of unfavorable long-term response to lithium in patients with BD. Our study underscores the potential of PGS analysis to contribute to predictive models for medication response in psychiatry. The results of our study support clinical observations that have pointed to better lithium responsiveness in a BD subtype characterized by lower psychiatric co-morbidity and more dominant mania-related clinical features.

Acknowledgements The authors are grateful to all patients who participated in the study and we appreciate the contributions of clinicians, scientists, research assistants and study staffs who have helped with patient recruitment, data collection and sample preparation for the studies. We are also indebted to the members of the ConLi+Gen Scientific Advisory Board (<http://www.conligen.org/>) for critical input over the course of the project. The analysis of this study was carried out using the high-performance computational capabilities of the University of Adelaide, Phoenix supercomputer <https://www.adelaide.edu.au/phoenix/>.

Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium Naomi R. Wray^{77,78}, Stephan Ripke^{79,80,81}, Manuel Mattheisen^{82,83,84,85}, Maciej Trzaskowski⁷⁷, Enda M. Byrne⁷⁷, Abdel Abdellaoui⁸⁶, Mark J. Adams⁸⁷, Esben Agerbo^{85,88,89}, Tracy M. Air⁹⁰, Till F. M. Andlauer^{91,92}, Silviu-Alin Bacanu⁹³, Marie Bækvad-Hansen^{85,94}, Aartjan T. F. Beekman⁹⁵, Tim B. Bigdeli^{93,96}, Elisabeth B. Binder^{91,97}, Douglas H. R. Blackwood⁸⁷, Julien Bryois⁹⁸, Henriette N. Buttenschøn^{84,85,99}, Jonas Bybjerg-Grauholm^{85,94}, Na Cai^{100,101}, Enrique Castelao¹⁰², Jane varregaard Christensen^{83,84,85}, Toni-Kim Clarke⁸⁷, Jonathan R. I. Coleman¹⁰³, Lucia Colodro-Conde¹⁰⁴, Baptiste Couvy-Duchesne^{105,106}, Nick Craddock¹⁰⁷, Gregory E. Crawford^{108,109}, Gail Davies¹¹⁰, Ian J. Deary¹¹⁰, Franziska Degenhardt^{111,112}, Eske M. Derks¹⁰⁴, Nese Direk^{113,114}, Conor V. Dolan⁸⁶, Erin C. Dunn^{115,116,117}, Thalia C. Eley¹⁰³, Valentina Escott-Price¹¹⁸, Farnush Farhadi Hassan

Kiadeh¹¹⁹, Hilary K. Finucane^{120,121}, Andreas J. Forstner^{111,112,122,123}, Josef Frank¹²⁴, Hélène A. Gaspar¹⁰³, Michael Gill¹²⁵, Fernando S. Goes¹²⁶, Scott D. Gordon¹²⁷, Jakob Grove^{83,84,85,128}, Lynsey S. Hall^{87,129}, Christine Søholm Hansen^{85,94}, Thomas F. Hansen^{130,131,132}, Stefan Herms^{111,112,123}, Ian B. Hickie¹³³, Per Hoffmann^{111,112,123}, Georg Homuth¹³⁴, Carsten Horn¹³⁵, Jouke-Jan Hottenga⁸⁶, David M. Hougaard^{85,94}, Marcus Ising¹³⁶, Rick Jansen⁹⁵, Eric Jorgenson¹³⁷, James A. Knowles¹³⁸, Isaac S. Kohane^{139,140,141}, Julia Kraft⁸⁰, Warren W. Kretschmar¹⁴², Jesper Krogh¹⁴³, Zoltán Kutalik^{144,145}, Yihan Li¹⁴², Penelope A. Lind¹⁰⁴, Donald J. MacIntyre^{146,147}, Dean F. MacKinnon¹²⁶, Robert M. Maier⁷⁸, Wolfgang Maier¹⁴⁸, Jonathan Marchini¹⁴⁹, Hamdi Mbarek⁸⁶, Patrick McGrath¹⁵⁰, Peter McGuffin¹⁰³, Sarah E. Medland¹⁰⁴, Divya Mehta^{78,151}, Christel M. Middeldorp^{86,152,153}, Evelin Mihailov¹⁵⁴, Yuri Milanecchi⁹⁵, Lili Milani¹⁵⁴, Francis M. Mondimore¹²⁶, Grant W. Montgomery⁷⁷, Sara Mostafavi^{155,156}, Niamh Mullins¹⁰³, Matthias Nauck^{157,158}, Bernard Ng¹⁵⁶, Michel G. Nivard⁸⁶, Dale R. Nyholt¹⁵⁹, Paul F. O'Reilly¹⁰³, Hogni Oskarsson¹⁶⁰, Michael J. Owen¹⁶¹, Jodie N. Painter¹⁰⁴, Carsten Bøcker Pedersen^{85,88,89}, Marianne Giørtz Pedersen^{85,88,89}, Roseann E. Peterson^{93,162}, Erik Pettersson⁹⁸, Wouter J. Peyrot⁹⁵, Giorgio Pistis¹⁰², Danielle Posthuma^{163,164}, Jorge A. Quiroz¹⁶⁵, Per Qvist^{77,84,85}, John P. Rice¹⁶⁶, Brien P. Riley⁹³, Margarita Rivera^{103,167}, Saira Saeed Mirza¹¹³, Robert Schoevers¹⁶⁸, Eva C. Schulte^{169,170}, Ling Shen¹³⁷, Jianxin Shi¹⁷¹, Stanley I. Shyn¹⁷², Engilbert Sigurdsson¹⁷³, Grant C. B. Sinnamon¹⁷⁴, Johannes H. Smit⁹⁵, Daniel J. Smith¹⁷⁵, Hreinn Stefansson¹⁷⁶, Stacy Steinberg¹⁷⁶, Fabian Streit¹²⁴, Jana Strohmaier¹²⁴, Katherine E. Tansey¹⁷⁷, Henning Teismann¹⁷⁸, Alexander Teumer¹⁷⁹, Wesley Thompson^{85,131,180,181}, Pippa A. Thomson¹⁸², Thorgerir E. Thorgeirsson¹⁷⁶, Matthew Traylor¹⁸³, Jens Treutlein¹²⁴, Vassily Trubetskoy⁸⁰, André G. Uitterlinden¹⁸⁴, Daniel Umbricht¹⁸⁵, Sandra Van der Auwera¹⁸⁶, Albert M. van Hemert¹⁸⁷, Alexander Viktorin⁹⁸, Peter M. Visscher^{77,78}, Yunpeng Wang^{85,131,181}, Bradley T. Webb¹⁸⁸, Shantel Marie Weinsheimer^{85,131}, Jürgen Wellmann¹⁷⁸, Gonke Willemsen⁸⁶, Stephanie H. Witt¹²⁴, Yang Wu⁷⁷, Hualin S. Xi¹⁸⁹, Jian Yang^{78,190}, Futao Zhang⁷⁷, Volker Arolt¹⁹¹, Bernhard T. Baune⁹⁰, Klaus Berger¹⁷⁸, Dorret I. Boomsma⁸⁶, Sven Cichon^{111,123,192,193}, Udo Dannlowski¹⁹¹, E. J. C. de Geus^{86,194}, J. Raymond DePaulo¹²⁶, Enrico Domenici¹⁹⁵, Katharina Domschke¹⁹⁶, Tõnu Esko^{81,154}, Hans J. Grabe¹⁸⁶, Steven P. Hamilton¹⁹⁷, Caroline Hayward¹⁹⁸, Andrew C. Heath¹⁶⁶, Kenneth S. Kendler⁹³, Stefan Kloiber^{136,199,200}, Glyn Lewis²⁰¹, Qingqi S. Li²⁰², Susanne Lucae¹³⁶, Pamela A. F. Madden¹⁶⁶, Patrik K. Magnusson⁹⁸, Nicholas G. Martin¹²⁷, Andrew M. McIntosh^{87,110}, Andres Metspalu^{154,203}, Ole Mors^{85,204}, Preben Bo Mortensen^{84,85,88,89}, Bertram Müller-Myhsok^{91,92,205}, Merete Nordentoft^{85,206}, Markus M. Nöthen^{111,112}, Michael C. O'Donovan¹⁶¹, Sara A. Paciga²⁰⁷, Nancy L. Pedersen⁹⁸, Brenda W. J. H. Penninx⁹⁵, Roy H. Perlis^{15,208}, David J. Porteous¹⁸², James B. Potash²⁰⁹, Martin Preisig¹⁰², Marcella Rietschel¹²⁴, Catherine Schaefer¹³⁷, Thomas G. Schulze^{124,170,210,211,212}, Jordan W. Smoller^{115,116,117}, Kari Stefansson^{176,213}, Henning Tiemeier^{113,214,215}, Rudolf Uher²¹⁶, Henry Völzke¹⁷⁹, Myrna M. Weissman^{150,217}, Thomas Werge^{85,131,218}, Cathryn M. Lewis^{103,219}, Douglas F. Levinson²²⁰, Gerome Breen^{103,221}, Anders D. Borglum^{83,84,85}, Patrick F. Sullivan^{98,222,223}

⁷⁷Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, Australia; ⁷⁸Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia; ⁷⁹Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA; ⁸⁰Department of Psychiatry and Psychotherapy, Universitätsmedizin Berlin Campus Charité Mitte, Berlin, DE, Germany; ⁸¹Medical and Population Genetics, Broad Institute, Cambridge, MA, USA; ⁸²Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; ⁸³Department of Biomedicine, Aarhus University, Aarhus, Denmark; ⁸⁴ISEQ, Centre for Integrative Sequencing, Aarhus University, Aarhus, Denmark; ⁸⁵PSYCH,

The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Copenhagen, Denmark; ⁸⁶Dept of Biological Psychology & EMGO+ Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; ⁸⁷Division of Psychiatry, University of Edinburgh, Edinburgh, GB, UK; ⁸⁸Centre for Integrated Register-based Research, Aarhus University, Aarhus, Denmark; ⁸⁹National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark; ⁹⁰Discipline of Psychiatry, University of Adelaide, Adelaide, SA, Australia; ⁹¹Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, DE, Germany; ⁹²Munich Cluster for Systems Neurology (SyNergy), Munich, DE, Germany; ⁹³Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA; ⁹⁴Center for Neonatal Screening, Department for Congenital Disorders, Statens Serum Institut, Copenhagen, Denmark; ⁹⁵Department of Psychiatry, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, the Netherlands; ⁹⁶Virginia Institute for Psychiatric and Behavior Genetics, Richmond, VA, USA; ⁹⁷Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA; ⁹⁸Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; ⁹⁹Department of Clinical Medicine, Translational Neuropsychiatry Unit, Aarhus University, Aarhus, Denmark; ¹⁰⁰Human Genetics, Wellcome Trust Sanger Institute, Cambridge, GB, UK; ¹⁰¹Statistical genomics and systems genetics, European Bioinformatics Institute (EMBL-EBI), Cambridge, GB, UK; ¹⁰²Department of Psychiatry, University Hospital of Lausanne, Prilly, Vaud, CH, Switzerland; ¹⁰³MRC Social Genetic and Developmental Psychiatry Centre, King's College London, London, GB, UK; ¹⁰⁴Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Herston, QLD, Australia; ¹⁰⁵Centre for Advanced Imaging, The University of Queensland, Saint Lucia, QLD, Australia; ¹⁰⁶Queensland Brain Institute, The University of Queensland, Saint Lucia, QLD, Australia; ¹⁰⁷Psychological Medicine, Cardiff University, Cardiff, GB, UK; ¹⁰⁸Center for Genomic and Computational Biology, Duke University, Durham, NC, USA; ¹⁰⁹Department of Pediatrics, Division of Medical Genetics, Duke University, Durham, NC, USA; ¹¹⁰Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, GB, UK; ¹¹¹Institute of Human Genetics, University of Bonn, Bonn, DE, Germany; ¹¹²Life&Brain Center, Department of Genomics, University of Bonn, Bonn, DE, Germany; ¹¹³Epidemiology, Erasmus MC, Rotterdam, Zuid-Holland, the Netherlands; ¹¹⁴Psychiatry, Dokuz Eylul University School of Medicine, Izmir, Turkey; ¹¹⁵Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA; ¹¹⁶Psychiatric and Neurodevelopmental Genetics Unit (PNGU), Massachusetts General Hospital, Boston, MA, USA; ¹¹⁷Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, USA; ¹¹⁸Neuroscience and Mental Health, Cardiff University, Cardiff, GB, UK; ¹¹⁹Bioinformatics, University of British Columbia, Vancouver, BC, Canada; ¹²⁰Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA; ¹²¹Department of Mathematics, Massachusetts Institute of Technology, Cambridge, MA, USA; ¹²²Department of Psychiatry (UPK), University of Basel, Basel, CH, Switzerland; ¹²³Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, CH, Switzerland; ¹²⁴Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Baden-Württemberg, DE, Germany; ¹²⁵Department of Psychiatry, Trinity College Dublin, Dublin, Ireland; ¹²⁶Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD, USA; ¹²⁷Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia; ¹²⁸Bioinformatics Research Centre, Aarhus University, Aarhus, Denmark; ¹²⁹Institute

of Genetic Medicine, Newcastle University, Newcastle upon Tyne, GB, UK; ¹³⁰Danish Headache Centre, Department of Neurology, Rigshospitalet, Glostrup, Denmark; ¹³¹Institute of Biological Psychiatry, Mental Health Center Sct. Hans, Mental Health Services Capital Region of Denmark, Copenhagen, Denmark; ¹³²PSYCH, The Lundbeck Foundation Initiative for Psychiatric Research, Copenhagen, Denmark; ¹³³Brain and Mind Centre, University of Sydney, Sydney, NSW, Australia; ¹³⁴Interfaculty Institute for Genetics and Functional Genomics, Department of Functional Genomics, University Medicine and Ernst Moritz Arndt University Greifswald, Greifswald, Mecklenburg-Vorpommern, DE, Germany; ¹³⁵Roche Pharmaceutical Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, CH, Switzerland; ¹³⁶Max Planck Institute of Psychiatry, Munich, DE, Germany; ¹³⁷Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA; ¹³⁸Psychiatry & The Behavioral Sciences, University of Southern California, Los Angeles, CA, USA; ¹³⁹Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA; ¹⁴⁰Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA; ¹⁴¹Informatics Program, Boston Children's Hospital, Boston, MA, USA; ¹⁴²Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, GB, UK; ¹⁴³Department of Endocrinology at Herlev University Hospital, University of Copenhagen, Copenhagen, Denmark; ¹⁴⁴Institute of Social and Preventive Medicine (IUMSP), University Hospital of Lausanne, Lausanne, VD, CH, Switzerland; ¹⁴⁵Swiss Institute of Bioinformatics, Lausanne, VD, CH, Switzerland; ¹⁴⁶Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, GB, UK; ¹⁴⁷Mental Health, NHS 24, Glasgow, GB, UK; ¹⁴⁸Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, DE, Germany; ¹⁴⁹Statistics, University of Oxford, Oxford, GB, UK; ¹⁵⁰Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, USA; ¹⁵¹School of Psychology and Counseling, Queensland University of Technology, Brisbane, QLD, Australia; ¹⁵²Child and Youth Mental Health Service, Children's Health Queensland Hospital and Health Service, South Brisbane, QLD, Australia; ¹⁵³Child Health Research Centre, University of Queensland, Brisbane, QLD, Australia; ¹⁵⁴Estonian Genome Center, University of Tartu, Tartu, Estonia; ¹⁵⁵Medical Genetics, University of British Columbia, Vancouver, BC, Canada; ¹⁵⁶Statistics, University of British Columbia, Vancouver, BC, Canada; ¹⁵⁷DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald, University Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE, Germany; ¹⁵⁸Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE, Germany; ¹⁵⁹Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, QLD, Australia; ¹⁶⁰Humus, Reykjavik, Iceland; ¹⁶¹MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, GB, UK; ¹⁶²Virginia Institute for Psychiatric & Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA; ¹⁶³Clinical Genetics, Vrije Universiteit Medical Center, Amsterdam, the Netherlands; ¹⁶⁴Complex Trait Genetics, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; ¹⁶⁵Solid Biosciences, Boston, MA, USA; ¹⁶⁶Department of Psychiatry, Washington University in Saint Louis School of Medicine, Saint Louis, MO, USA; ¹⁶⁷Department of Biochemistry and Molecular Biology II, Institute of Neurosciences, Center for Biomedical Research, University of Granada, Granada, Spain; ¹⁶⁸Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; ¹⁶⁹Department of Psychiatry and Psychotherapy, Medical Center of the University of Munich, Campus Innenstadt, Munich, DE, Germany; ¹⁷⁰Institute of Psychiatric Phenomics and Genomics (IPPG), Medical

Center of the University of Munich, Campus Innenstadt, Munich, DE, Germany; ¹⁷¹Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA; ¹⁷²Behavioral Health Services, Kaiser Permanente Washington, Seattle, WA, USA; ¹⁷³Faculty of Medicine, Department of Psychiatry, University of Iceland, Reykjavik, IS, Iceland; ¹⁷⁴School of Medicine and Dentistry, James Cook University, Townsville, QLD, Australia; ¹⁷⁵Institute of Health and Wellbeing, University of Glasgow, Glasgow, GB, UK; ¹⁷⁶deCODE Genetics / Amgen, Reykjavik, Iceland; ¹⁷⁷College of Biomedical and Life Sciences, Cardiff University, Cardiff, GB, UK; ¹⁷⁸Institute of Epidemiology and Social Medicine, University of Münster, Münster, Nordrhein-Westfalen, DE, Germany; ¹⁷⁹Institute for Community Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE, Germany; ¹⁸⁰Department of Psychiatry, University of California, San Diego, San Diego, CA, USA; ¹⁸¹KG Jebsen Centre for Psychosis Research, Norway Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway; ¹⁸²Medical Genetics Section, CGEM, IGMM, University of Edinburgh, Edinburgh, GB, UK; ¹⁸³Clinical Neurosciences, University of Cambridge, Cambridge, GB, UK; ¹⁸⁴Internal Medicine, Erasmus MC, Rotterdam, Zuid-Holland, the Netherlands; ¹⁸⁵Roche Pharmaceutical Research and Early Development, Neuroscience, Ophthalmology and Rare Diseases Discovery & Translational Medicine Area, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, CH, Switzerland; ¹⁸⁶Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE, Germany; ¹⁸⁷Department of Psychiatry, Leiden University Medical Center, Leiden, the Netherlands; ¹⁸⁸Virginia Institute of Psychiatric & Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA; ¹⁸⁹Computational Sciences Center of Emphasis, Pfizer Global Research and Development, Cambridge, MA, USA; ¹⁹⁰Institute for Molecular Bioscience, Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia; ¹⁹¹Department of Psychiatry, University of Münster, Münster, Nordrhein-Westfalen, DE, Germany; ¹⁹²Institute of Medical Genetics and Pathology, University Hospital Basel, University of Basel, Basel, CH, Switzerland; ¹⁹³Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, Juelich, DE, Germany; ¹⁹⁴Amsterdam Public Health Institute, Vrije Universiteit Medical Center, Amsterdam, the Netherlands; ¹⁹⁵Centre for Integrative Biology, Università degli Studi di Trento, Trento, Trentino-Alto Adige, Italy; ¹⁹⁶Department of Psychiatry and Psychotherapy, Medical Center, University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, DE, Germany; ¹⁹⁷Psychiatry, Kaiser Permanente Northern California, San Francisco, CA, USA; ¹⁹⁸Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, GB, UK; ¹⁹⁹Department of Psychiatry, University of Toronto, Toronto, ON, Canada; ²⁰⁰Centre for Addiction and Mental Health, Toronto, ON, Canada; ²⁰¹Division of Psychiatry, University College London, London, GB, UK; ²⁰²Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Titusville, NJ, USA; ²⁰³Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia; ²⁰⁴Psychosis Research Unit, Aarhus University Hospital, Risskov, Aarhus, Denmark; ²⁰⁵University of Liverpool, Liverpool, GB, UK; ²⁰⁶Mental Health Center Copenhagen, Copenhagen University Hospital, Copenhagen, Denmark; ²⁰⁷Human Genetics and Computational Biomedicine, Pfizer Global Research and Development, Groton, CT, USA; ²⁰⁸Psychiatry, Harvard Medical School, Boston, MA, USA; ²⁰⁹Psychiatry, University of Iowa, Iowa City, IA, USA; ²¹⁰Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, USA; ²¹¹Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Goettingen, Niedersachsen, DE, Germany; ²¹²Human Genetics

Branch, NIMH Division of Intramural Research Programs, Bethesda, MD, USA; ²¹³Faculty of Medicine, University of Iceland, Reykjavik, Iceland; ²¹⁴Child and Adolescent Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, the Netherlands; ²¹⁵Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, the Netherlands; ²¹⁶Psychiatry, Dalhousie University, Halifax, NS, Canada; ²¹⁷Division of Epidemiology, New York State Psychiatric Institute, New York, NY, USA; ²¹⁸Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; ²¹⁹Department of Medical & Molecular Genetics, King's College London, London, GB, UK; ²²⁰Psychiatry & Behavioral Sciences, Stanford University, Stanford, CA, USA; ²²¹NIHR BRC for Mental Health, King's College London, London, GB, UK; ²²²Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; ²²³Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Funding ATA received a Postgraduate Research Scholarship support from the University of Adelaide through the Adelaide Scholarship International (ASI) program. We thank 23andMe, Inc. staffs for giving us the permission to utilize GWAS summary data for depression which was included as part of the Psychiatric Genomics Consortium (PGC) study. The primary sources of funding were the Deutsche Forschungsgemeinschaft (DFG; grant no. RI 908/7-1; grant FOR2107, RI 908/11-1 to MR, NO 246/10-1 to MMN, WI3429/3-1 to SHW) and the Intramural Research Program of the National Institute of Mental Health (ZIA-MH00284311; ClinicalTrials.gov identifier: NCT00001174). The genotyping was in part funded by the German Federal Ministry of Education and Research (BMBF) through the Integrated Network IntegraMent (Integrated Understanding of Causes and Mechanisms in Mental Disorders), under the auspices of the e:Med Programme (grants awarded to TGS, MR, and MMN). Some data and biomaterials were collected as part of eleven projects (Study 40) that participated in the National Institute of Mental Health (NIMH) Bipolar Disorder Genetics Initiative. From 2003–2007, the Principal Investigators and Co-Investigators were: Indiana University, Indianapolis, IN, R01 MH59545, John Nurnberger, M.D., Ph.D., Marvin J. Miller, M.D., Elizabeth S. Bowman, M.D., N. Leela Rau, M.D., P. Ryan Moe, M.D., Nalini Samavedy, M.D., Rif El-Mallakh, M.D. (at University of Louisville), Hussein Manji, M.D. (at Johnson and Johnson), Debra A. Glitz, M.D. (at Wayne State University), Eric T. Meyer, Ph.D., M.S. (at Oxford University, UK), Carrie Smiley, R.N., Tatiana Foroud, Ph.D., Leah Flury, M.S., Danielle M. Dick, Ph.D. (at Virginia Commonwealth University), Howard Edenberg, Ph.D.; Washington University, St. Louis, MO, R01 MH059534, John Rice, Ph.D., Theodore Reich, M.D., Allison Goate, Ph.D., Laura Bierut, M.D. K02 DA21237; Johns Hopkins University, Baltimore, M.D., R01 MH59533, Melvin McInnis, M.D., JRD, M.D., Dean F. MacKinnon, M.D., FMM, M.D., JBP, M.D., PPZ, Ph.D., Dimitrios Avramopoulos, and Jennifer Payne; University of Pennsylvania, PA, R01 MH59553, Wade Berrettini, M.D., Ph.D.; University of California at San Francisco, CA, R01 MH60068, William Byerley, M. D., and Sophia Vinogradov, M.D.; University of Iowa, IA, R01 MH059548, William Coryell, M.D., and Raymond Crowe, M.D.; University of Chicago, IL, R01 MH59535, Elliot Gershon, M.D., Judith Badner, Ph.D., Francis McMahon, M.D., Chunyu Liu, Ph.D., Alan Sanders, M.D., Maria Caserta, Steven Dinwiddie, M.D., Tu Nguyen, Donna Hrakal; University of California at San Diego, CA, R01 MH59567, JK, M.D., Rebecca McKinney, B.A.; Rush University, IL, R01 MH059556, William Scheftner, M.D., Howard M. Kravitz, D.O., M.P.H., Diana Marta, B.S., Annette Vaughn-Brown, M.S.N., R.N., and Laurie Bederow, M.A.; NIMH Intramural Research Program, Bethesda, MD, 1Z01MH002810-01, FJM, M.D., LK, Psy.D., Sevilla Detera-Wadleigh, Ph.D., Lisa Austin, Ph.D., Dennis L. Murphy, M.D.; Howard University, William B. Lawson, M.D., Ph.D., Evarista Nwulia, M.D., and Maria Hipolito, M.D. This work was supported by the NIH grants P50CA89392 from the National Cancer Institute and 5K02DA021237

from the National Institute of Drug Abuse. The Canadian part of the study was supported by the Canadian Institutes of Health Research to MA grant #64410 to MA. Collection and phenotyping of the Australian UNSW sample, by PBM, PRS, JMF and AW, was funded by an Australian NHMRC Program Grant (No.1037196)), with personnel supported by NHMRC project grants (Nos. 1063960, 1066177) and the Janette Mary O'Neil Research Fellowship to JMF. The collection of the Barcelona sample was supported by the Centro de Investigación en Red de Salud Mental (CIBERSAM), IDIBAPS, the CERCA Programme / Generalitat de Catalunya, Miguel Servet II and Instituto de Salud Carlos III (grant numbers PI080247, PI1200906, PI12/00018, 2017 SGR 1577 and 2017 SGR 1365). Dr FC was funded by unrestricted funding from CIBERSAM and "Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 134), Generalitat de Catalunya (Government of Catalonia). The Swedish Research Council, the Stockholm County Council, Karolinska Institutet and the Söderström-Königsk Foundation supported this research through grants awarded to LB, LF, CL and MS. The collection of the Geneva sample was supported by the Swiss National Foundation (grants Synapsy 51NF40-158776 and 32003B-125469). The work by the French group was supported by INSERM (Institut National de la Santé et de la Recherche Médicale); AP-HP (Assistance Publique des Hôpitaux de Paris); the Fondation FondaMental (RTRS Santé Mentale) and the labex Bio-PSY (Investissements d'Avenir program managed by the ANR under reference ANR-11-IDEX-0004-02). The German Research Foundation (DFG, grant FOR2107 DA1151/5-1 and DA1151/5-2 to UD; SFB-TRR58, Project C09 and Z02 to UD), and the Interdisciplinary Center for Clinical Research (IZKF) of the Medical Faculty of the University of Münster (grant Dan3/012/17 to UD) supported this work. The collection of the Romanian sample was supported by U.E.F.I.S.C.D.I., Romania, grant awarded to MG-S. The collection of the Czech sample was supported by the project No. LO1611 with a financial support from the MEYS under the NPU I program and by the Czech Science Foundation, grant No. 17-07070S.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

- Ferrari AJ, Stockings E, Khoo JP, Erskine HE, Degenhardt L, Vos T, et al. The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013. *Bipolar Disord*. 2016;18:440–50.
- Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. *World Psychiatry*. 2014;13:153–60.
- Schulze TG, Alda M, Adli M, Akula N, Ardaur R, Bui ET, et al. The International Consortium on Lithium Genetics (ConLiGen): an initiative by the NIMH and IGSLI to study the genetic basis of response to lithium treatment. *Neuropsychobiology*. 2010;62:72–8.
- Malhi GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust N Z J Psychiatry*. 2015;49:1087–206.
- Hou L, Heilbronner U, Degenhardt F, Adli M, Akiyama K, Akula N, et al. Genetic variants associated with response to lithium treatment in bipolar disorder: a genome-wide association study. *The Lancet*. 2016;387:1085–93.
- Grof P, Duffy A, Cavazzoni P, Grof E, Garnham J, MacDougall M, et al. Is response to prophylactic lithium a familial trait? *J Clin Psychiatry*. 2002;63:942–7.
- Garnham J, Munro A, Slaney C, Macdougall M, Passmore M, Duffy A, et al. Prophylactic treatment response in bipolar disorder: results of a naturalistic observation study. *J Affect Disord*. 2007;104:185–90.
- Lahteenvuo M, Tanskanen A, Taipale H, Hoti F, Vattulainen P, Vieta E, et al. Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a Finnish nationwide cohort of patients with bipolar disorder. *JAMA Psychiatry*. 2018;75:347–55.
- Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. *Lancet* (London, England). 2016;387:1561–72.
- Bauer M, Gitlin M. Practical management of lithium. In: *The essential guide to lithium treatment*. Springer International Publishing: Cham, 2016, pp 113–28.
- Oedegaard KJ, Alda M, Anand A, Andreassen OA, Balaraman Y, Berrettini WH, et al. The Pharmacogenomics of Bipolar Disorder study (PGBD): identification of genes for lithium response in a prospective sample. *BMC Psychiatry*. 2016;16:129.
- Severus E, Taylor MJ, Sauer C, Pfennig A, Ritter P, Bauer M, et al. Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. *Int J Bipolar Disord*. 2014;2:15.
- Joas E, Karanti A, Song J, Goodwin GM, Lichtenstein P, Landén M. Pharmacological treatment and risk of psychiatric hospital admission in bipolar disorder. *Br J Psychiatry*. 2017;210:197–202.
- Chen CH, Lee CS, Lee MT, Ouyang WC, Chen CC, Chong MY, et al. Variant GADL1 and response to lithium therapy in bipolar I disorder. *N Engl J Med*. 2014;370:119–28.
- Song J, Bergen SE, Di Florio A, Karlsson R, Charney A, Ruderfer DM, et al. Genome-wide association study identifies SESTD1 as a novel risk gene for lithium-responsive bipolar disorder. *Molecular Psychiatry*. 2016;21:1290–7.
- Amare AT, Schubert KO, Hou L, Clark SR, Papiol S, Heilbronner U, et al. Association of polygenic score for schizophrenia and HLA antigen and inflammation genes with response to lithium in bipolar affective disorder: a genome-wide association study. *JAMA Psychiatry*. 2018;75:65–74.
- Goldberg JF, Gamo JL, Leon AC, Kocsis JH, Portera L. A history of substance abuse complicates remission from acute mania in bipolar disorder. *J Clin Psychiatry*. 1999;60:733–40.
- Calkin C, van de Velde C, Ruzickova M, Slaney C, Garnham J, Hajek T, et al. Can body mass index help predict outcome in patients with bipolar disorder? *Bipolar Disorders*. 2009;11:650–6.
- Calkin CV, Ruzickova M, Uher R, Hajek T, Slaney CM, Garnham JS, et al. Insulin resistance and outcome in bipolar disorder. *Brit J Psychiatry*. 2015;206:52–7.
- Mitchell PB, Frankland A, Hadzi-Pavlovic D, Roberts G, Corry J, Wright A, et al. Comparison of depressive episodes in bipolar disorder and in major depressive disorder within bipolar disorder pedigrees. *Brit J Psychiatry*. 2011;199:303–9.
- Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM. Cross-Disorder Group of the Psychiatric Genomics C et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet*. 2013;45:984–94.
- Cross-Disorder Group of the Psychiatric Genomics C. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *The Lancet*. 2013;381:1371–9.
- Amare AT, Schubert KO, Klingler-Hoffmann M, Cohen-Woods S, Baune BT. The genetic overlap between mood disorders and cardiometabolic diseases: a systematic review of genome wide and candidate gene studies. *Transl Psychiatry*. 2017;7:e1007.
- Amare AT, Schubert KO, Baune BT. Pharmacogenomics in the treatment of mood disorders: strategies and opportunities for personalized psychiatry. *EPMA J*. 2017;8:211–27.

25. Abou-Saleh MT, Muller-Oerlinghausen B, Coppen AJ. Lithium in the episode and suicide prophylaxis and in augmenting strategies in patients with unipolar depression. *Int J Bipolar Disord*. 2017;5:11.
26. Zhou X, Ravindran AV, Qin B, Del Giovane C, Li Q, Bauer M, et al. Comparative efficacy, acceptability, and tolerability of augmentation agents in treatment-resistant depression: systematic review and network meta-analysis. *J Clin Psychiatry*. 2015;76:e487–98.
27. Tiihonen J, Tanskanen A, Hoti F, Vattulainen P, Taipale H, Mehtala J, et al. Pharmacological treatments and risk of readmission to hospital for unipolar depression in Finland: a nationwide cohort study. *Lancet Psychiatry*. 2017;4:547–53.
28. Popovic D, Reinares M, Goikolea JM, Bonnin CM, Gonzalez-Pinto A, Vieta E. Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder. *Eur Neuropsychopharmacol*. 2012;22:339–46.
29. Vieta E, Berk M, Schulze TG, Carvalho AF, Suppes T, Calabrese JR, et al. Bipolar disorders. *Nat Rev Dis Primers*. 2018;4:18008.
30. Colom F, Vieta E, Daban C, Pacchiarotti I, Sanchez-Moreno J. Clinical and therapeutic implications of predominant polarity in bipolar disorder. *J Affect Disord*. 2006;93:13–7.
31. Kessing LV, Hellmund G, Andersen PK. Predictors of excellent response to lithium: results from a nationwide register-based study. *Int Clin Psychopharmacol*. 2011;26:323–8.
32. Kleindienst N, Engel R, Greil W. Which clinical factors predict response to prophylactic lithium? A systematic review for bipolar disorders. *Bipolar Disorders*. 2005;7:404–17.
33. Pfennig A, Schlattmann P, Alda M, Grof P, Glenn T, Muller-Oerlinghausen B, et al. Influence of atypical features on the quality of prophylactic effectiveness of long-term lithium treatment in bipolar disorders. *Bipolar Disorders*. 2010;12:390–6.
34. Fountoulakis KN, Kontis D, Gonda X, Siamouli M, Yatham LN. Treatment of mixed bipolar states. *Int J Neuropsychopharmacol*. 2012;15:1015–26.
35. Sportiche S, Geoffroy PA, Brichant-Petitjean C, Gard S, Khan JP, Azorin JM, et al. Clinical factors associated with lithium response in bipolar disorders. *Aust N Z J Psychiatry*. 2017;51:524–30.
36. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature Genetics* 2018;50:668–81.
37. Duffy A, Alda M, Milin R, Grof P. A consecutive series of treated affected offspring of parents with bipolar disorder: is response associated with the clinical profile? *Can J Psychiatry*. 2007;52:369–76.
38. Manchia M, Adli M, Akula N, Arda R, Aubry JM, Backlund L, et al. Assessment of response to lithium maintenance treatment in bipolar disorder: a consortium on lithium genetics (ConLiGen) report. *PloS ONE*. 2013;8:e65636.
39. Scott J, Etain B, Manchia M, Brichant-Petitjean C, Geoffroy PA, Schulze T et al. An examination of the quality and performance of the Alda scale for classifying lithium response phenotypes. *Bipolar Disorders*. 2019. <https://doi.org/10.1111/bdi.12829>.
40. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 2007;81:559–75.
41. Das S, Forer L, Schonherr S, Sidore C, Locke AE, Kwong A, et al. Next-generation genotype imputation service and methods. *Nat Genet*. 2016;48:1284–7.
42. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. 2009;460:748–52.
43. Stahl EA, Breen G, Forstner AJ, McQuillin A, Ripke S, Trubetskoy V, et al. Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat Genet*. 2019;51:793–803.
44. Zheng HF, Forgetta V, Hsu YH, Estrada K, Rosello-Diez A, Leo PJ, et al. Whole-genome sequencing identifies EN1 as a determinant of bone density and fracture. *Nature*. 2015;526:112–7.
45. Amare AT, Vaez A, Hsu YH, Direk N, Kamali Z, Howard DM et al. Bivariate genome-wide association analyses of the broad depression phenotype combined with major depressive disorder, bipolar disorder or schizophrenia reveal eight novel genetic loci for depression. *Mol Psychiatry*. 2019. <https://doi.org/10.1038/s41380-018-0336-6>.
46. Choi SW, O'Reilly PF. PRSice-2: polygenic risk score software for biobank-scale data. *GigaScience*. 2019;8:giz082.
47. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. *BMJ*. 1995;310:170.
48. Malhi GS, Tanious M, Das P, Berk M. The science and practice of lithium therapy. *Aust N Z J Psychiatry*. 2012;46:192–211.
49. Grof E, Haag M, Grof P, Haag H. Lithium response and the sequence of episode polarities: preliminary report on a Hamilton sample. *Prog Neuropsychopharmacol Biol Psychiatry*. 1987;11:199–203.
50. Hui TP, Kandola A, Shen L, Lewis G, Osborn DPJ, Geddes JR, et al. A systematic review and meta-analysis of clinical predictors of lithium response in bipolar disorder. *Acta Psychiatr Scand*. 2019;140:94–115.
51. Grof P, Alda M, Grof E, Zvolosky P, Walsh M. Lithium response and genetics of affective disorders. *J Affect Disord*. 1994;32:85–95.
52. Bschor T. Lithium in the treatment of major depressive disorder. *Drugs*. 2014;74:855–62.
53. Alevizos B, Alevizos E, Leonardou A, Zervas I. Low dosage lithium augmentation in venlafaxine resistant depression: an open-label study. *Psychiatriki*. 2012;23:143–8.
54. Bauer M, Döpfner S. Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. *Prim Care Companion J Clin Psych*. 2000;2:31.
55. Bauer M, Adli M, Ricken R, Severus E, Pilhatsch M. Role of lithium augmentation in the management of major depressive disorder. *CNS Drugs*. 2014;28:331–42.
56. Bauer M, Bschor T, Kunz D, Berghofer A, Strohle A, Muller-Oerlinghausen B. Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. *Am J Psychiatry*. 2000;157:1429–35.
57. Bauer M, Adli M, Baethge C, Berghöfer A, Sasse J, Heinz A, et al. Lithium augmentation therapy in refractory depression: clinical evidence and neurobiological mechanisms. *Can J Psychiatry*. 2003;48:440–8.
58. Bschor T, Bauer M. Efficacy and mechanisms of action of Lithium augmentation in refractory major depression. *Curr Pharm Des*. 2006;12:2985–92.
59. Kan C, Pedersen NL, Christensen K, Bornstein SR, Licinio J, MacCabe JH, et al. Genetic overlap between type 2 diabetes and depression in Swedish and Danish twin registries. *Mol Psychiatry*. 2016;21:903.
60. Bigdeli TB, Ripke S, Peterson RE, Trzaskowski M, Bacanu SA, Abdellaoui A, et al. Genetic effects influencing risk for major depressive disorder in China and Europe. *Transl Psychiatry*. 2017;7:e1074.
61. Shan GW, Makmor-Bakry M, Omar MS. Long term use of lithium and factors associated with treatment response among patients with bipolar disorder. *Psychiatr Danub*. 2016;28:146–53.
62. Wray NR, Lee SH, Mehta D, Vinkhuyzen AA, Dudbridge F, Middeldorp CM. Research review: polygenic methods and their application to psychiatric traits. *J Child Psychol Psychiatry Allied Discip*. 2014;55:1068–87.

Affiliations

Azmeraw T. Amare ^{1,2} · Klaus Oliver Schubert ^{1,3} · Liping Hou ⁴ · Scott R. Clark¹ · Sergi Papiol ^{5,6} · Micah Cearns ¹ · Urs Heilbronner ^{5,7} · Franziska Degenhardt⁸ · Fasil Tekola-Ayele⁹ · Yi-Hsiang Hsu^{10,11} · Tatyana Shekhtman¹² · Mazda Adli¹³ · Nirmala Akula⁴ · Kazufumi Akiyama¹⁴ · Raffaella Ardau¹⁵ · Bárbara Arias¹⁶ · Jean-Michel Aubry¹⁷ · Lena Backlund^{18,19} · Abesh Kumar Bhattacharjee¹² · Frank Bellivier²⁰ · Antonio Benabarre²¹ · Susanne Bengesser²² · Joanna M. Biernacka ^{23,24} · Armin Birner²² · Clara Brichant-Petitjean²⁰ · Pablo Cervantes²⁵ · Hsi-Chung Chen ²⁶ · Caterina Chillotti¹⁵ · Sven Cichon^{8,27} · Cristiana Cruceanu ²⁸ · Piotr M. Czerski ²⁹ · Nina Dalkner²² · Alexandre Dayer¹⁷ · Maria Del Zompo³⁰ · J. Raymond DePaulo³¹ · Bruno Étain ²⁰ · Stephane Jamain ³² · Peter Falkai⁶ · Andreas J. Forstner ^{8,27,33} · Louise Frisen^{18,19} · Mark A. Frye²⁴ · Janice M. Fullerton ^{34,35} · Sébastien Gard³⁶ · Julie S. Garnham ³⁷ · Fernando S. Goes³¹ · Maria Grigoriou-Serbanescu ³⁸ · Paul Grof³⁹ · Ryota Hashimoto ^{40,41} · Joanna Hauser²⁹ · Stefan Herms ^{8,27} · Per Hoffmann^{8,27} · Andrea Hofmann⁸ · Esther Jiménez ²¹ · Jean-Pierre Kahn⁴² · Layla Kassem⁴ · Po-Hsiu Kuo⁴³ · Tadafumi Kato ⁴⁴ · John R. Kelsoe ¹² · Sarah Kittel-Schneider⁴⁵ · Sebastian Kliwiczki⁴⁶ · Barbara König⁴⁷ · Ichiro Kusumi ⁴⁸ · Gonzalo Laje⁴ · Mikael Landén ^{49,50} · Catharina Lavebratt ^{18,19} · Marion Leboyer⁵¹ · Susan G. Leckband⁵² · Alfonso Tortorella⁵³ · Mirko Manchia^{54,55} · Lina Martinsson⁵⁶ · Michael J. McCarthy ^{12,57} · Susan L. McElroy⁵⁸ · Francesc Colom^{59,60} · Marina Mitjans^{16,60,61} · Francis M. Mondimore³¹ · Palmiero Monteleone^{62,63} · Caroline M. Nievergelt ¹² · Markus M. Nöthen⁸ · Tomas Novák ⁶⁴ · Claire O'Donovan³⁷ · Norio Ozaki ⁶⁵ · Urban Ösby⁶⁶ · Andrea Pfennig⁶⁷ · James B. Potash³¹ · Andreas Reif ⁴⁵ · Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium · Eva Reininghaus²² · Guy A. Rouleau⁶⁸ · Janusz K. Rybakowski⁴⁶ · Martin Schalling^{18,19} · Peter R. Schofield ^{34,35} · Barbara W. Schweizer³¹ · Giovanni Severino³⁰ · Paul D. Shilling¹² · Katzutaka Shimoda⁶⁹ · Christian Simhandl⁷⁰ · Claire M. Slaney³⁷ · Alessio Squassina ³⁰ · Thomas Stamm¹³ · Pavla Stopkova ⁶⁴ · Mario Maj⁶³ · Gustavo Turecki ²⁸ · Eduard Vieta²¹ · Julia Veeh⁴⁵ · Stephanie H. Witt ⁷¹ · Adam Wright⁷² · Peter P. Zandi⁷³ · Philip B. Mitchell ⁷² · Michael Bauer ⁶⁷ · Martin Alda ^{37,64} · Marcella Rietschel ⁷¹ · Francis J. McMahon ⁴ · Thomas G. Schulze^{4,5,7,31,71} · Bernhard T. Baune^{74,75,76}

¹ Discipline of Psychiatry, School of Medicine, University of Adelaide, Adelaide, SA, Australia

² South Australian Academic Health Science and Translation Centre, South Australian Health and Medical Research Institute (SAHMRI), Adelaide, SA, Australia

³ Northern Adelaide Local Health Network, Mental Health Services, Adelaide, SA, Australia

⁴ Intramural Research Program, National Institute of Mental Health, National Institutes of Health, US Department of Health & Human Services, Bethesda, MD, USA

⁵ Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany

⁶ Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University Munich, Munich, Germany

⁷ Department of Psychiatry and Psychotherapy, University Medical Center (UMG), Georg-August University Göttingen, Göttingen, Germany

⁸ Institute of Human Genetics, University of Bonn and Department of Genomics, Life & Brain Center, Bonn, Germany

⁹ Epidemiology Branch, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA

¹⁰ HSL Institute for Aging Research, Harvard Medical School, Boston, MA, USA

¹¹ Program for Quantitative Genomics, Harvard School of Public Health, Boston, MA, USA

¹² Department of Psychiatry, University of California San Diego, San Diego, CA, USA

¹³ Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin Berlin, Campus Charité Mitte, Berlin, Germany

¹⁴ Department of Biological Psychiatry and Neuroscience, Dokkyo Medical University School of Medicine, Mibu, Tochigi, Japan

¹⁵ Unit of Clinical Pharmacology, Hospital University Agency of Cagliari, Cagliari, Italy

¹⁶ Unitat de Zoologia i Antropologia Biològica (Dpt. Biologia Evolutiva, Ecologia i Ciències Ambientals), Facultat de Biologia and Institut de Biomedicina (IBUB), University of Barcelona, CIBERSAM, Barcelona, Spain

¹⁷ Department of Psychiatry, Mood Disorders Unit, HUG - Geneva University Hospitals, Geneva, Switzerland

¹⁸ Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden

¹⁹ Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden

²⁰ INSERM UMR-S 1144, Université Paris Diderot, Département de Psychiatrie et de Médecine Addictologique, AP-HP, Groupe Hospitalier Saint-Louis-Lariboisière-F.Widal, Paris, France

- 21 Bipolar Disorder Program, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain
- 22 Department of Psychiatry and Psychotherapeutic Medicine, Research Unit for bipolar affective disorder, Medical University of Graz, Graz, Austria
- 23 Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA
- 24 Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA
- 25 The Neuromodulation Unit, McGill University Health Centre, Montreal, QC, Canada
- 26 Department of Psychiatry & Center of Sleep Disorders, National Taiwan University Hospital, Taipei, Taiwan
- 27 Human Genomics Research Group, Department of Biomedicine, University Hospital Basel, Basel, Switzerland
- 28 Douglas Mental Health University Institute, McGill University, Montreal, QC, Canada
- 29 Psychiatric Genetic Unit, Poznan University of Medical Sciences, Poznan, Poland
- 30 Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy
- 31 Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, USA
- 32 Inserm U955, Translational Psychiatry laboratory, Fondation FondaMental, Créteil, France
- 33 Department of Psychiatry (UPK), University of Basel, Basel, Switzerland
- 34 Neuroscience Research Australia, Sydney, NSW, Australia
- 35 School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia
- 36 Service de psychiatrie, Hôpital Charles Perrens, Bordeaux, France
- 37 Department of Psychiatry, Dalhousie University, Halifax, NS, Canada
- 38 Biometric Psychiatric Genetics Research Unit, Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, Romania
- 39 Mood Disorders Center of Ottawa, Ottawa, ON, Canada
- 40 Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Osaka, Japan
- 41 Department of Psychiatry, Osaka University Graduate School of Medicine, Osaka, Japan
- 42 Service de Psychiatrie et Psychologie Clinique, Centre Psychothérapique de Nancy - Université de Lorraine, Nancy, France
- 43 Department of Public Health & Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan
- 44 Laboratory for Molecular Dynamics of Mental Disorders, RIKEN Center for Brain Science, Saitama, Japan
- 45 Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt, Germany
- 46 Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland
- 47 Department of Psychiatry and Psychotherapeutic Medicine, Landesklinikum Neunkirchen, Neunkirchen, Austria
- 48 Department of Psychiatry, Hokkaido University Graduate School of Medicine, Sapporo, Japan
- 49 Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the Gothenburg University, Gothenburg, Sweden
- 50 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
- 51 Inserm U955, Translational Psychiatry laboratory, Université Paris-Est-Créteil, Department of Psychiatry and Addictology of Mondor University Hospital, AP-HP, Fondation FondaMental, Créteil, France
- 52 Office of Mental Health, VA San Diego Healthcare System, San Diego, CA, USA
- 53 Department of Psychiatry, University of Perugia, Perugia, Italy
- 54 Section of Psychiatry, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy
- 55 Department of Pharmacology, Dalhousie University, Halifax, NS, Canada
- 56 Department of Clinical Neurosciences, Karolinska Institutet, Stockholm, Sweden
- 57 Department of Psychiatry, VA San Diego Healthcare System, San Diego, CA, USA
- 58 Department of Psychiatry, Lindner Center of Hope / University of Cincinnati, Mason, OH, USA
- 59 Mental Health Research Group, IMIM-Hospital del Mar, Barcelona, Catalonia, Spain
- 60 Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain
- 61 Clinical Neuroscience, Max Planck Institute of Experimental Medicine, Göttingen, Germany
- 62 Neurosciences Section, Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Salerno, Italy
- 63 Department of Psychiatry, University of Campania "Luigi Vanvitelli", Naples, Italy
- 64 National Institute of Mental Health, Klecany, Czech Republic
- 65 Department of Psychiatry & Department of Child and Adolescent Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, Japan

-
- ⁶⁶ Department of Neurobiology, Care Sciences, and Society, Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden
- ⁶⁷ Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Medical Faculty, Technische Universität Dresden, Dresden, Germany
- ⁶⁸ Montreal Neurological Institute and Hospital, McGill University, Montreal, QC, Canada
- ⁶⁹ Department of Psychiatry, Dokkyo Medical University School of Medicine, Mibu, Tochigi, Japan
- ⁷⁰ Bipolar Center Wiener Neustadt, Sigmund Freud University, Medical Faculty, Vienna, Austria
- ⁷¹ Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany
- ⁷² School of Psychiatry, University of New South Wales, and Black Dog Institute, Sydney, NSW, Australia
- ⁷³ Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
- ⁷⁴ Department of Psychiatry and Psychotherapy, University of Münster, Münster, Germany
- ⁷⁵ Department of Psychiatry, Melbourne Medical School, University of Melbourne, Parkville, VIC, Australia
- ⁷⁶ The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia